

LONG-TERM TREATMENT WITH TOFACITINIB IN SEVERE ALOPECIA AREATA: AN UPDATE

Dear Editor:

Tofacitinib is a Janus kinase (JAK) 1/3 inhibitor that has been approved by the United States Food and Drug Administration for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. An increasing number of studies have demonstrated the efficacy of tofacitinib in treatment of alopecia areata (AA).^{1–6} Treatment duration in these studies ranges from 2 to 18 months. Durability is short, with shedding occurring a mean 8.5 weeks after discontinuation.³ Less is known about extended tofacitinib administration. Here, we update our previous findings with a series of severe AA patients receiving long-term treatment with oral tofacitinib.⁶

METHODS

The relevant institutional review board approved this retrospective chart review. Investigators searched Cleveland Clinic records for patients with AA treated with tofacitinib from February 2015 to September 2017. Prior to initiation, all other AA therapies were stopped. Patient history and physical examination were obtained before starting treatment. Baseline laboratory evaluation findings, including complete metabolic panel, complete blood count, lipid panel, human immunodeficiency virus screen, hepatitis screen, and quantiferon gold test, were also obtained before tofacitinib initiation. Because no tofacitinib monitoring guidelines currently exist, laboratory results were collected every 3 to 4 months and quantiferon tuberculosis test findings were collected annually. Women of childbearing potential, barring any contraindication, were recommended to start oral contraception per their primary care providers. Hair loss was measured using the Severity of Alopecia Tool (SALT), which considers the sum of percent hair loss in varying areas of the scalp where a higher score means a greater amount of hair loss. SALT scores were calculated at baseline and each visit by the same physician, at which time standardized photos were also taken. Patients were treated by four different physicians. Tofacitinib was initiated at 5mg twice daily, increased by 5mg per month, and held at



FIGURE 1. A 38-year-old woman with severe alopecia areata treated with tofacitinib citrate 10mg twice daily—A) Baseline, B) Month 9, C) Month 12, and D) Month 20

TABLE 1. Patient demographics, disease severity and tofacitinib therapy

Patient	Sex	Age at Treatment Initiation	Race	Disease Duration (years)	Last Hair Growth (years)	First Signs of Hair Growth (months)	Therapy Duration (months)	Maintenance Dose (mg/day, split BID)
1	F	57	Caucasian	25	1	3	22	20
2	F	43	Caucasian	19	4	3	15	20
3	F	22	Caucasian	16	4	3	17	15
4	F	55	African American	26	4	7	28	15
5	F	39	Caucasian	13	1	0	0.5	10
6	F	56	Caucasian	16	2	10	26	20
7	F	62	Caucasian	7	1	3	7	20
8	F	46	Caucasian	36	3	3	3	10
9	F	57	Caucasian	15	1	3	12	20
10	F	37	African American	9	3	4	15	10
11	F	57	Caucasian	9	7	8	24	20
12	F	55	African American	31	1	3	6	10
13	F	50	African American	1	0 (disease onset within previous 14 months)	6	12	10
14	F	38	Caucasian	7	1	1	20	20
15	F	56	Caucasian	11	1	2	25	25
16	M	25	Caucasian	5	2	3	4	10
17	M	54	Caucasian	3	2	2	12	20
18	F	56	Caucasian	16	6	2	5	10
19	F	49	African American	17	1	8	13	10
20	F	61	Caucasian	44	1	3	4	10

AA: Alopecia areata; F: Female; M: Male; BID: Twice daily

the dose when the treating physician noted regrowth or when a daily dose of up to 25mg was reached. Regrowth was defined as the presence of new terminal hairs at sites devoid of hair prior to treatment. Adverse events were recorded at each visit. Continuous variables were described using medians and standard deviations, while categorical variables were described using counts and percentages.

RESULTS

A retrospective cohort of 20 patients was treated. Patients were mostly female (90%) and more likely to have thyroid disease and atopy, compared to the general population (65% and 40%, respectively, of our cohort). All 20 patients had a diagnosis of alopecia areata—90 percent had more severe subtypes (70% alopecia universalis, 20% alopecia totalis)—with a mean baseline SALT score of 88 percent. The average length of the current episode of alopecia was 2.4 years.

Twelve patients (60%) received tofacitinib for at least 12 months. Patients were treated for an average of 13 months (range: 0.5–28 months). Maintenance doses ranged from 10mg to 25mg, with the majority of patients taking 20mg in split daily doses.

The average time to regrowth was 3.85 months. Three months after initiating treatment, 70 percent of patients showed regrowth. Regrowth ranged from 1 to 100 percent, with a mean percent regrowth of 42.6 percent and a median of 55 percent. Eleven patients (55%) achieved an improvement in SALT score greater than 50 percent. Twenty-five percent of patients achieved full regrowth (>90% improvement in SALT score) during the study period. Among patients treated for more than 12 months, 91.7 percent had regrowth by the end of the study period. Three patients were nonresponders, with a less than five-percent improvement in SALT score.

Seven patients developed lab abnormalities. Four patients experienced dose-dependent cholesterol, triglycerides, and/or low-density lipoprotein elevation. These resolved with dose decrease or continued treatment, though one patient was started on a statin. Six clinical adverse events (e.g., palpitations, herpes zoster, upper respiratory infection) occurred, each in a different patient. See Tables 1 and 2 for patient characteristics, including demographics, disease, treatment course, and outcomes.

TABLE 2. Response to tofacitinib therapy for alopecia areata and associated lab abnormalities and clinical adverse events

Patient	Treatment Initiation SALT Score	Final Data Collection SALT Score	Regrowth (%) at Time of Last Appointment	Lab Abnormality, Associated Dose, and Outcome	Clinical Adverse Event, Associated Dose, and Outcome
1	100	30.8	69.0	Hypercholesterolemia (cholesterol 217, triglyceride 147, LDL 143) at baseline, worsening by Month 8 (cholesterol 250, triglyceride 288, LDL 153); dosage 20mg; started on atorvastatin by PCP at Month 9 with improvement of cholesterol (151), triglycerides (178) and LDL (68)	Herpes zoster at Month 6; dosage 20mg; drug discontinued for 10 days then restarted at same dose
2	78.3	32.2	59.0	NA	NA
3	100	50.6	49.0	NA	NA
4	100	50.6	49.0	AKI (Cr 1.5 from baseline 1.1) and elevated total cholesterol 270 (150–220), LDL 175 (<130) at Month 4; dosage 30mg	NA
5	95	44	50.0	NA	Morbilloform eruption and peripheral edema Week 2 after therapy; dosage 20mg; medication discontinued immediately; edema/eruption resolved within one week after discontinuation
6	100	95	5.0	NA	NA
7	100	95	5.0	NA	URI at Month 2; medication discontinued for 30 days then resumed; no shedding noted at that time; lost to follow-up
8	79.3	44.2	40.0	NA	NA
9	76	3	96.0	NA	NA
10	100	98	2.0	AST/ALT elevation (AST43/ALT48) at Month 6, but 2 months after dose increase to 25mg (15mg qAM and 10mg qPM); medication discontinued but AST remained elevated (49); patient rechallenged with 10mg, with further AST elevation (80); recommendation to discontinue medication	NA
11	100	20	80.0	Elevated cholesterol (211) at Month 6; dosage 20mg; medication continued; cholesterol normalized by Month 24 without intervention	NA
12	100	1	99.0	NA	Chest palpitations at Month 6; dosage 10mg; medication discontinued; patient later found to be on a higher than necessary dose of levothyroxine, which was corrected
13	95	0	100.0	NA	NA
14	50	0	100.0	Leukopenia (WBC 3.5) at Month 12; dosage 20mg; dose reduced to 5mg BID and patient lost hair growth; medication increased back to 10mg BID with patient informed of risks, WBC normalized to 4.1 by Month 12	NA
15	71.6	38	47.0	NA	NA
16	100	100	0.0 (scant regrowth on face noted at Month 3; lost to follow-up)	NA	NA
17	100	50	50.0	Elevated total cholesterol (215), LDL (135) and total bilirubin 1.8 (0–1) at Month 3; dosage 20mg; dose decreased to 10mg; LDL and total cholesterol normalized by Month 6, then dose increased to 20mg without further lab abnormalities; later diagnosed by hepatologist with Gilbert's syndrome	NA
18	90	47.2	48.0	NA	Recurrent URIs from initiation through Month 5; dosage 15mg (10mg qAM/5 mg qPM); medication stopped then restarted at Month 7 at 10mg daily without further URI symptoms
19	50	0	100.0	Elevated AST/ALT (48/53) at Month 10; dosage 10mg; patient chose to continue medication upon normalization of values	NA
20	100	100	10.0	NA	NA

AA: alopecia areata; F: female; M: male; PCP: primary care provider; LDL: low-density lipoprotein; NA: not applicable; SALT: Severity of Alopecia Tool; AKI: acute kidney injury; AST: aspartate aminotransferase; ALT: alanine aminotransferase; qAM: every morning; qPM: every afternoon; WBC: white blood cells; BID: twice daily; URI: upper respiratory infection

DISCUSSION

The majority of patients experienced hair regrowth, ranging from less than 5 percent to 100 percent regrowth during the study. This is consistent with other studies, suggesting disease duration might not predict patient response, but rather a pathophysiological mechanism might be involved.² For several patients, regrowth differed from their natural hair color and texture (Figure 1). One patient demonstrated female androgenetic alopecia with regrowth, a finding previously observed in male patients.⁴

As this is an off-label use of tofacitinib, this medication was obtained for most patients only after an extensive appeal process with insurance companies. Of the 20 patients treated, six experienced medication interruption—four due to adverse effects and two due to lapses in prescription insurance coverage. Durability among our population was shorter than the 10 to 12 weeks reported in other studies, with hair shedding occurring 4 to 5 weeks after discontinuation, suggesting that a short amount of time is needed for AA inflammatory pathways to reestablish themselves following discontinuation of medication.

Our study is limited by its small sample size, precluding detailed subgroup analyses. Larger, randomized, controlled trials are needed to explore such variations in regrowth. Nevertheless, our results suggest JAK inhibition might serve as an effective treatment modality for AA.

With regard,

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